1 STATISTICAL ASPECTS

1.1 Description of statistical methods to be used including the timetable for the planned interim analyses

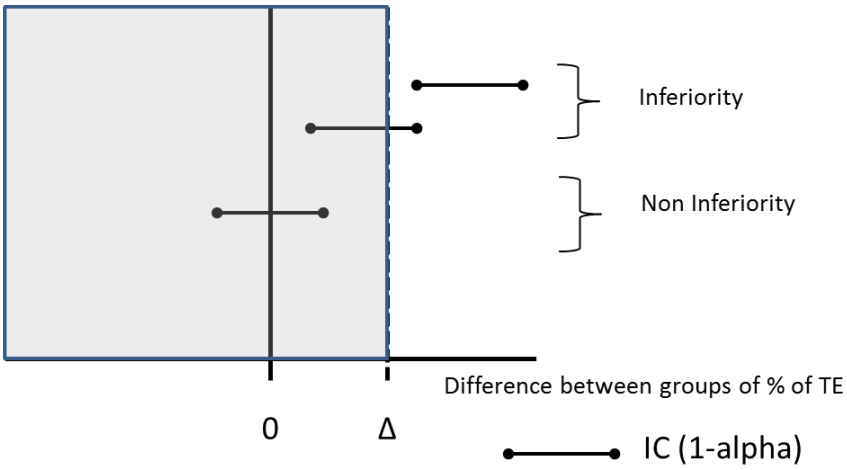
No interim analysis is planned.

Baseline caracteristics of patients will be described according to group of intervention. Continuous variables will be summarized using descriptive statistics, i.e number of subjects, mean, median, standard deviation (s.d), inter quartile range, minimum and maximum. Qualitative variables will be summarized by frequency and percentage.

Principal criteria analysis:

Since this is a non-inferiority study, analysis of the principal criterion will be performed on per protocol population. Secondary analysis will be performed on ITT population. Thrombo-embolic event (TE event) will be defined by: DVT (assessed by proximal compression ultrasonography) or PE (a CTPA or angiography showing intraluminal defect, or a Ventilation/Perfusion lung scan showing a high-probability pattern). The decision rule will be based on the upper bound of the 90% two sided confidence interval of the difference of percentage of TE events between groups.

If the upper bound of the confidence interval is above the 1.5% of difference, the non inferiority hypothesis of the intervention group will be rejected. Dunnett and Gent chisquare test will also be performed.



Secondary analysis will be performed on ITT population. Considering cluster randomization, confirmatory analysis will be performed using generalized estimating

equation (GEE) assuming an exchangeable correlation matrix structure and considering clustering at site level. Secondary criteria will be compared under superiority hypothesis and on ITT population. Descriptive analysis will be performed. Superiority approach will be used to compare secondary evaluation criteria between groups. The ED length stay and the mean of hospital admission following the ED visit will be compared using mixed model considering center as random effect.

Unnecessary irradiative imaging, adverse events and Deaths at 3 months will be compared using generalized estimating equation (GEE) assuming an exchangeable correlation matrix structure and considering clustering at site level.

1.2 Calculation hypotheses for the number of subjects required and the result

According to recent large European cohorts, we estimate that the rate of primary endpoint in our control group will be 1.5% [32,33,48].

To be regarded as non-inferior, the maximal difference in proportions between two groups (Delta) should not exceed 1.5% - an absolute rate of primary event of 3% in the intervention group. This failure rate corresponds to the upper bound of observed rate after a negative CPTA and is a widely accepted criterion for the validation of diagnostic strategies for PE [49].This rate is in line with previous landmark studies that comprise the basis of our current understanding.

Sample size under non inferiority hypothesis:

To assess non inferiority of the “PERC strategy”, with alpha = 5%, beta=20%, one sided, N1= 1624 subjects are needed (East 6, Cytel).

Cluster design effect hypothesis:

A cluster is a 6 months period for one site.

Intra class correlation coefficient (ICCC)=0.002

Mean cluster size (m)= 60 patients

Cluster design effect: D= (1+(m-1)xICCC)=1.118

Sample size taking cluster design effect into account:

Sample size needed = D x N1 = 1815 patients

With 15 sites that is 30 clusters, 61 subjects per site per period are required and will lead to 1830 subjects.

1.3 Anticipated level of statistical significance

Non inferiority analysis cf. above.

All superiority test will be performed at 5%.

1.4 Statistical criteria for termination of the research.

Not applicable

1.5 Method for taking into account missing, unused or invalid data

Missing data will not be replaced except for the principal criteria for the secondary ITT analysis. Missing value will be considered as an event whatever the group randomized.

1.6 Management of modifications made to the analysis plan for the initial strategy.

Modification made in analysis will be documented in the final report.

1.7 Selection of populations

Per protocol population: real strategy applied whatever the group allocated

ITT population: sites according to the randomized group even if the strategy allocated was not applied.

<u>Modifications made to the analysis plan – May 2017:</u>

Since there is only one TE event observed at month 3 in the per protocol population, generalized estimating equation was not performed for the analysis of the principal criterion and the Dunett p-value could not be calculated.

Secondary objectives were analysed as follow: qualitative variables were compared using Pearson's chi-square test or Fisher exact test and continuous variables were compared using a Wilcoxon rank-sum test. The prevalence of PE at baseline was compared using Pearson's chi-square test or Fisher exact test.

<u>Posthoc sensitivity analyses – December 2017:</u>

There was an inclusion bias leading to a different profile of patients in the two groups: more very low risk patients were included in the PERC group, as can be seen in regards to the rate of PERC negative patients in the two groups: 48% in the PERC group and 38% in the control group.

We performed two posthoc sensitivity analyses with the aim of comparing groups of patients with the same risk of PE.

The first posthoc sensitivity analysis was made after removing a random sample (computer generated) of 150 PERC negative patients in the PERC group. The second one was made after the addition of 175 PERC negative patients to the control group. The same statistical plan was used for these posthoc analyses.